

Neuroendocrine responses to fenfluramine and its relationship to personality in alcoholism*

H.-G. Weijers¹, G. A. Wiesbeck¹, F. Jakob², and J. Böning¹

¹Addiction Research Group, Department of Psychiatry and Psychotherapy, and

²Department of Metabolism, Endocrinology and Molecular Medicine, Medical Polyclinic, University Hospital of Würzburg, Federal Republic of Germany

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Summary. This study investigates the relationship between personality and serotonergic reactivity in alcohol dependence. Personality characteristics were assessed according to the Temperament and Character model of Cloninger, the five-factor model of McCrae and Costa, Zuckerman's Sensation Seeking as well as Eysenck's impulsiveness/venturesomeness. Placebo-controlled prolactin response to the serotonin (5-HT) reuptake inhibitor/releaser fenfluramine served as an indicator for the reactivity of serotonergic neurotransmission. Forty abstinent alcohol-dependent men were subdivided into high and low prolactin responders according to their level of neuroendocrine response. High responders were characterized by decreased harm avoidance while their extraversion and venturesomeness scores were increased in comparison to low responders. The data demonstrates that harm avoidance on the one hand and extraversion/venturesomeness on the other are inversely correlated to serotonergic neurotransmission. These results support a specific relationship between personality traits and the serotonergic system.

Keywords: Personality, prolactin, fenfluramine, serotonin, harm avoidance, extraversion, venturesomeness.

Introduction

The use of pharmacological substances as “research tools” is sometimes preferable to other methods. For example, they can easily be applied to humans while other forms of manipulation are often out of favor for ethical reasons. They allow an in vivo application which is most closely related to the normal state of the individual. Further advantages are the variability of dosage, the

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reversibility of effects and a theoretical foundation allowing the formulation of hypotheses based on the mode of pharmacological action.

When used in "challenge tests", pharmacological substances with a specific receptor profile allow the stimulation of this specific receptor system. The response evoked may then serve as a parameter for the reactivity of the system challenged.

Due to the fact that brain mechanisms are involved in personality traits, drug-challenge responses have been widely used to study the relationship between personality and the reactivity of neurochemical systems. Several biopsychological models of personality emphasize the relationships between personality and the monoamine neurotransmitters (e.g. Cloninger, 1987; Depue et al., 1994; Zuckerman, 1994).

Monoaminergic mechanisms and personality traits are also associated with alcoholism. Cloninger (1987), for example, originally hypothesized that dopamine is the major neuromodulator of novelty seeking and that harm avoidance refers to serotonin (5-HT). A large body of evidence, in both clinical and preclinical studies, demonstrates a role for serotonergic dysregulation in the etiology of alcoholism (see LeMarquand et al., 1994, for review). Clearly, pharmacological substances have been widely used to investigate neurochemical correlates of personality and behavior especially in alcoholism. For example, "craving" for alcohol has been investigated with various pharmacological substances as research tools like *m*-chlorophanylpiperazin (Buydens-Branchey et al., 1997), dextrometorphan (Soyka et al., 2000) or apomorphine (Wiesbeck et al., 2000). Various dimensions of behavior and personality, like anxiety, nervousness, depression, psychopathology during withdrawal or sensation seeking, have also been investigated in alcoholics using drug-challenge designs (Krystal et al., 1996; Wiesbeck et al., 1996a,b; Fahlke et al., 1999). Among male alcoholics with no Axis I diagnoses and 2 weeks of abstinence, Lee and Meltzer (1991), for example, reported a diminished prolactin response to MK212, a direct-acting serotonin 5HT₂/5HT_{1c} agonist.

However, studies relating 5-HT-induced endocrine responses to personality traits are rare. Netter et al. (1998), for example, reported that high aggression was associated with blunted prolactin responses after *d*-fenfluramine. In a more recently published study of the same group, it could be shown that the prolactin response after *d*-fenfluramine is related to Cloninger's harm avoidance. Healthy male volunteers with blunted responses revealed higher scores in this personality dimension (Hennig et al., 2000).

The 5-HT reuptake inhibitor/releaser fenfluramine is one of the most intensively studied substances used in challenge paradigms. It is a potent and specific serotonergic substance that exerts its effects by stimulating the release of serotonin and then inhibiting its reuptake (Garattini et al., 1987; Gorard et al., 1993). In so doing, it reliably induces marked responses in serum prolactin dose-dependently (Quattrone et al., 1983), an effect that has been used as a neuroendocrine parameter to investigate the relationship between serotonergic reactivity and personality in healthy subjects (Hennig et al., 2000) as well as to study the sensitivity of serotonergic receptors in various psychiatric

disorders (Herpertz et al., 1997; Thakore et al., 1996; Bancroft and Cook, 1995; Myers et al., 1994; O'Keane and Dinan, 1991; Targum and Marshall, 1989; Lopez-Ibor et al., 1988). In alcoholism, fenfluramine has been used to investigate alcohol consumption and alcohol withdrawal in animals (Halladay et al., 2000) and prolactin response in humans. For example, a blunted prolactin response was found in response to fenfluramine in adult alcoholics after 2 weeks of abstinence (Farren et al., 1995) and among chronic, heavy drinkers with no abstinence (Balldin et al., 1994).

Adolescents with early-onset alcoholism do not demonstrate the diminished prolactin response to fenfluramine characteristic of adult alcoholics with impulsive-aggression (Soloff et al., 2000).

So far, there has been no data on neuroendocrine response to fenfluramine in abstinent alcoholics nor has there been an investigation of the relationship between fenfluramine-induced serotonergic responsivity and the individual personality characteristics of patients.

The present study will address the question whether the prolactin response after fenfluramine is related to a broad spectrum of personality dimensions in detoxified alcoholic men. Taking into consideration the model of Cloninger (1987) and the results of Hennig et al. (2000), we hypothesize that subjects with low prolactin responses after fenfluramine should exhibit higher scores in harm avoidance than subjects with high prolactin responses after fenfluramine.

Methods

Subjects

Male patients diagnosed with long-term primary alcohol dependence were included in the study. Each patient had to meet at least 5 of 8 ICD-10 criteria for dependence. They all gave their informed written consent before participating in the study. Also prior to inclusion in the study, all subjects underwent clinical detoxification according to routine procedures at the Department of Psychiatry, University of Würzburg, Germany.

Subjects were not included in the study if they reported a history of illegal drug use, or if they were tested drug-positive on the urine test administered at the time of admission or during their in-patient treatment. Further reasons for exclusion were psychiatric comorbidity, axis-II disorder and severe neurological or medical disorders. All patients were Caucasian and native German speakers. The sociodemographic characteristics of the subjects are summarized in Table 1. Their main characteristics of alcohol dependence are depicted in Table 2.

Neuroendocrine test procedure

Responsivity to serotonergic challenge was assessed with d,l-fenfluramine. Neuroendocrine testing was performed with a single blind placebo-controlled design during the 7th week of in-patient treatment. At this point individuals were fully detoxified and devoid of any symptoms of prolonged withdrawal. They were drug-free and carefully controlled for abstinence. The challenge-test took place under standardized conditions: patients received three tablets of Ponderax® (Itherapia GmbH, München, Germany), each containing 20 mg fenfluraminhydrochloride, always at 8.30 and on empty stomachs. Placebo doses had been administered approximately one week before. Blood samples were drawn at 8 different times: immediately before taking the tablets (0 min) as well as at intervals of 30, 60, 90, 120, 150, 180, and 210 minutes thereafter.

Table 1. Demographic characteristics of the total sample and comparisons between high and low prolactin responders to d,l-fenfluramine

	Total sample (n = 40)	Prolactin response		
		Low (n = 20)	High (n = 20)	P ^a
<i>Gender</i>				
Women	–	–	–	–
Men	40 (100) ^b	20 (50)	20 (50)	
<i>Age</i>				
M	40.1	42.3	38.0	
S.D.	8.0	7.9	7.8	.087
range	24–58	25–58	24–56	
<i>Family status</i>				
Married	17 (43)	9 (45)	8 (40)	
Single	9 (23)	4 (20)	5 (25)	
Widowed	1 (2)	1 (5)	0 (0)	.679
Divorced/separated	13 (32)	6 (30)	7 (35)	
<i>Household</i>				
Living alone	19 (47)	9 (45)	10 (50)	
Living together with a partner	21 (53)	11 (55)	10 (50)	.516
<i>Highest grade in school</i>				
Without graduation	2 (5)	2 (10)	0 (0)	
Elementary school	27 (68)	14 (70)	13 (65)	
Junior high school	6 (15)	2 (10)	4 (20)	.290
High-school	2 (5)	0 (0)	2 (10)	
University	3 (7)	2 (10)	1 (5)	
<i>Occupational status</i>				
Employed	21 (53)	11 (55)	10 (50)	
Unemployed	19 (47)	9 (45)	10 (50)	.473

^a Statistical comparison between low responders and high responders; P-values of χ^2 -tests and P-values of t-tests for independent samples (age; two-tailed). ^b Values in parentheses are percentages

Plasma levels of prolactin were measured using a commercially available solid phase chemiluminescence-enzyme-immunoassay (Prolaktin-Immulite®, DPC, Biermann, Bad Nauheim, Germany). The mean intra- and interassay variation coefficients were 6.5 and 8.5% respectively. The lower limit of detection was 0.5 ng/ml (10.6 μ U/ml). Normal values are 2.5–17 ng/ml in men. To obtain μ U/ml from ng/ml values are multiplied by a factor of 21.2.

The neuroendocrinological data was evaluated using repeated measures analysis of variance with the two within-subject factors drug (fenfluramine vs. placebo) and time (t0, t30, t60, t90, t120, t150, t180, t210). These RMANOVAS were tested for lack of sphericity; Greenhouse-Geisser adjustments were made to the degrees of freedom. Significant drug x time interaction was followed by post-hoc comparisons between fenfluramine and placebo at the different time points using paired t-tests.

Using this procedure, the onset of the fenfluramine effect was defined as that point of time after drug application when prolactin responses between fenfluramine and placebo started to differ significantly ($P < .05$) and remained so until the last measurement. This period was defined as “period of response”. “Prolactin response” was calculated as the difference of the areas under the curves (AUC) between fenfluramine and placebo within the “period of response”. The AUC’s were calculated using the trapezoid rule. On the

Table 2. Main characteristics for alcohol dependence of the total sample and comparisons between high and low prolactin responders to d,l-fenfluramine

	Total sample (n = 40)		Prolactin response				
	M	S.D.	Low (n = 20)		High (n = 20)		P ^a
			M	S.D.	M	S.D.	
<i>Number of ICD-10 criteria for alcohol dependence fulfilled</i>							
Total	5.6	1.8	5.7	1.7	5.6	1.9	.957
Psychic dependence	2.3	0.9	2.3	0.9	2.3	0.9	.900
Somatic dependence	3.4	1.2	3.4	1.2	3.3	1.2	.861
Age at alcoholism onset (ICD-10) (years)	27.1	9.4	27.6	9.9	26.7	9.2	.768
<i>Duration of alcohol dependence</i>							
(Age at admission minus onset) (years)	13.0	8.5	14.7	8.8	11.3	8.1	.204
γ -Glutamyl-Transferase (γ -GT) at admission (U/l)	108.8	117.8	138.7	139.4	85.0	94.2	.199
Mean Corpuscular Volume (MCV) at admission (fl)	95.0	4.7	94.9	4.3	95.2	5.2	.877
<i>Alcohol intake before detoxification</i>							
(Average number of drinks per day during the three months prior to admission)	23.0	9.1	24.0	9.5	22.1	8.9	.506
<i>Withdrawal Syndrome Scale</i>							
(weighted score)	1.8	1.7	1.5	1.0	2.2	2.2	.209
<i>Munich Alcoholism Test</i>							
(weighted score)	30.0	7.8	28.8	7.7	31.2	7.9	.356
<i>Family history for alcoholism</i>							
Positive	23		14		9		
Negative	17		6		11		.146

^aComparison between low responders and high responders; P-values of t-tests for independent samples (two-tailed) and P-values of a χ^2 -tests (family history)

basis of this response, the sample was divided into "high" (prolactin response above the sample median) and "low" (prolactin response below the sample median) responders using the median-split procedure.

Although initially designed as part of the research project called "Clinical and neuro-biological multi-level analysis of biological subgroups of alcoholics in cross section" within the "Würzburg BMBF Addiction Research Association", this part of the study had to be cancelled immediately after the removal of d,l-fenfluramine from the general market.

Personality assessment

The self-report questionnaire measures used included assessment of personality characteristics based on the five-factor model of McCrae and Costa, the Temperament and Character model of Cloninger, as well as Zuckerman's Sensation Seeking and Eysenck's impulsiveness/venturesomeness.

NEO-FFI Personality Inventory. The German version of the NEO-FFI (Borkenau and Ostendorf, 1993) is a 60-item self-rating questionnaire intended to operationalize the five-factor model of personality (Costa and McCrae, 1989). It was developed with rational and factor-analytic methods to measure the five factors of neuroticism (NEO-N), (NEO-E), openness to experience (NEO-O), agreeableness (NEO-A), and conscientiousness (NEO-C) on five scales consisting of 12 items each.

Temperament- and Character-Inventory (TCI). The Temperament- and Character-Inventory (Cloninger et al., 1994), a 226-item, true-false self-rating questionnaire, is an expanded version of Cloninger's Tridimensional Personality Questionnaire based on a psychobiological model of the structure and development of personality (Cloninger, 1987; Cloninger et al., 1993). Together with 12 subscores, scores for four temperament dimensions – novelty seeking, harm avoidance, reward dependence and persistence – and three character dimensions, i.e. self-directedness, cooperativeness, and self-transcendence, are supplied. In the present study we used the German version of this questionnaire as translated by Richter et al. (2001). Because of the psychometric deficiencies of most subscales (Weijers et al., 1999), subscores are not taken into account in the further analysis.

Impulsiveness-Venturesomeness-Empathy Scale (I7). The German version of the I7 (Eysenck et al., 1990) is a 47-item self-report questionnaire. It yields three independent scores for impulsiveness (I7-Imp), venturesomeness (I7-Vent), and empathy (I7-Emp). I7-Imp reflects poor behavioral control and lack of ability to delay gratification; I7-Ven reflects sensation seeking and sociability; and I7-Emp reflects sensitivity to the feelings and reactions of others as well as susceptibility to social cues (Weyers et al., 1995).

Sensation Seeking Scale (SSS). We used a German translation (Department of Psychology at the University of Gießen, Germany) of the fifth version (SSS-V) of Zuckerman's Sensation Seeking Scale (Zuckerman et al., 1978). The 40-item self-report questionnaire contains four scales of 10 items each: thrill and adventure seeking (SSS-TAS: predilection for risky sports), experience seeking (SSS-ES: predilection for trying out new things), disinhibition (SSS-DIS: predilection for being unrestrained) and boredom susceptibility (SSS-BS: the inability to endure event-poor, boring and monotonous situations). Items with explicit reference to addiction were excluded from the present analysis (SSS-ES: Item 10 and 14; SSS-DIS: Item 11, 23 and 39). A total score (SSS-TOT) was computed by adding the four subscale-scores.

The different self-rating scales were administered individually after at least 28 days of in-patient treatment. At this time all participants were fully detoxified and devoid of any symptoms of prolonged withdrawal. They were carefully controlled for abstinence and were not under psychoactive medication.

Statistical analysis

In accordance with our hypothesis, the difference between high and low prolactin responders in harm avoidance was evaluated using one-tailed significance testing by a t-test for independent samples at the $\alpha = 0.05$ probability level. All the other differences in personality measures between high and low prolactin responders were tested by using multiple t-tests for independent samples. For unequal variances ($P < .20$, Levene-Test) between the response groups, approximated t-values and degrees of freedom were used. To evaluate the significance of these differences we adjust the alpha-level of $\alpha = 0.05$ by executing the Holm-procedure. The statistical analyses were implemented using SPSS for Windows 10.0.

Results

High and low prolactin responders did not differ significantly in any socio-demographic characteristic (Table 1), nor could we find any evidence for a

relationship between the clinical data relating to alcoholism, drinking behavior, the alcohol-dependence syndrome, and the data pertaining to the prolactin response after fenfluramine (Table 2).

The two-way ANOVA comparing prolactin responses between fenfluramine and placebo over time revealed a significant effect for "drug" ($F_{(1,38)} = 33.0$, $P < .000$), a significant effect for "time" ($F_{(4,169)} = 23.7$, $P < .000$), and a significant "drug" $\times$ "time" interaction ($F_{(4,141)} = 34.6$, $P < .000$). Focusing on the total sample, prolactin levels fell slightly over the time under placebo while they increased under fenfluramine from t120 to t210: statistically significant differences were detected at t150, t180 and t210. Therefore, the period between t150 and t210 was defined as the "period of response" and the sample was divided into high and low responders as described above.

The repeated-measures three way ANOVA comparing prolactin responses to fenfluramine and placebo over the eight time points between high and low responders demonstrates that the three-way interaction became highly significant ($F_{(7,32)} = 3.4$; $P < .01$). It yielded an effect size explaining about 40% of the total variance ($\eta^2 = 0.44$). Therefore we can conclude that our response classification procedure clearly differentiates subjects with high from those with low prolactin response after challenge with fenfluramine.

The time course of prolactin changes according to the drug condition and response classification is depicted in Fig. 1. It demonstrates that differences in prolactin response were more pronounced in high responders than in low responders (per definition). However, in high responders the difference between the two curves became statistically significant already at t120 (in low responders t150).

Means and standard deviations of personality dimensions according to the response classification are given in Table 3. The results of the statistical

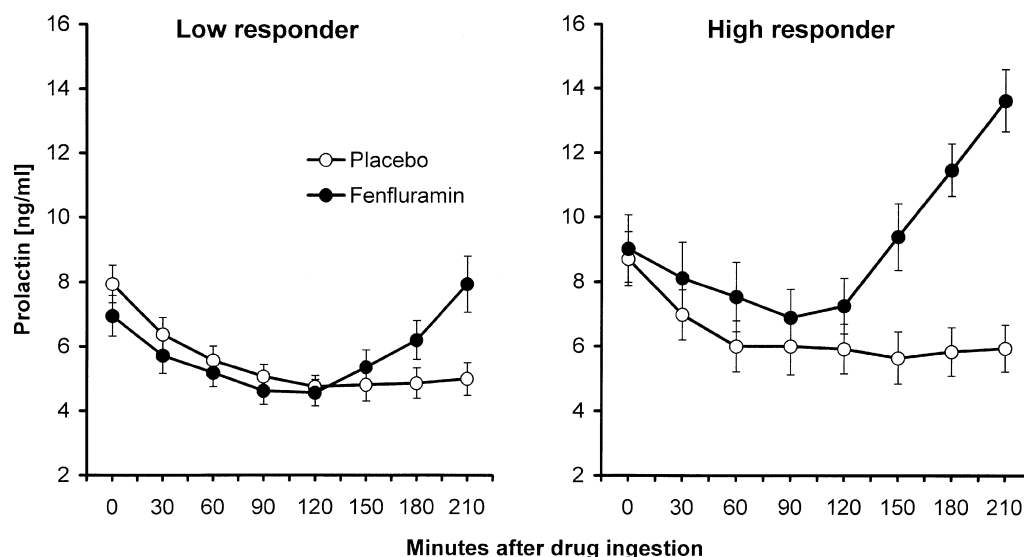


Fig. 1. Means ($\pm$ S. E. M.) of prolactin concentration according to drug (60mg d,l-fenfluramine vs. placebo) and response classification

Table 3. Personality and prolactin responses to d,l-fenfluramine in abstinent alcoholic men

	Prolactin-Response				
	Low (n = 20)		High (n = 20)		P ^a
	M	S.D.	M	S.D.	
<i>Temperament- and Character-Inventory</i>					
Harm Avoidance	18.9	7.9	13.5	6.0	.020
Novelty Seeking	19.7	5.0	21.8	6.3	.247
Reward Dependence	14.1	4.0	13.4	3.9	.565
Persistence	3.5	2.2	4.4	1.9	.147
Self-Directedness	28.5	6.4	31.3	7.8	.224
Cooperativeness	30.2	6.6	30.9	4.8	.687
Self-Transcendence	11.2	6.4	12.8	7.4	.472
<i>NEO-FFI Personality Inventory</i>					
Neuroticism	2.1	0.5	1.7	0.6	.084
Extraversion	2.0	0.4	2.4	0.5	.008
Openness to Experience	2.2	0.3	2.3	0.6	.394
Agreeableness	2.4	0.4	2.3	0.4	.453
Conscientiousness	2.6	0.5	2.7	0.4	.648
<i>Impulsiveness-Venturesomeness-Empathy Scale</i>					
Impulsiveness	8.3	2.7	8.9	2.3	.451
Venturesomeness	7.7	2.6	10.1	2.4	.003
Empathy	7.6	3.8	8.8	3.6	.284
<i>Sensation Seeking Scale</i>					
Sensation Seeking (Total)	16.5	6.0	19.0	4.8	.156
Thrill and Adventure Seeking	4.7	3.2	6.2	3.2	.133
Experience Seeking	4.6	1.4	4.7	1.5	.714
Disinhibition	3.5	1.6	4.0	2.0	.385
Boredom Susceptibility	3.9	2.4	4.1	1.8	.713

^aStatistical comparison between low responders and high responders; P-values of t-tests for independent samples (two-tailed)

comparison between the two response groups revealed that prolactin response after fenfluramine was significantly related to harm avoidance (TCI), extraversion (NEO-FFI) and venturesomeness (I7): low responders revealed significantly higher scores in harm avoidance and lower scores in extraversion and venturesomeness than high responders.

There was a tendency toward higher scores among low responders in all subscales of harm avoidance which was most pronounced for the second subscale (fear of uncertainty; high responders: M/S.D. = 3.4/1.9, low responders: M/S.D. = 4.8/2.0; $t_{(38)} = 2.3$, $P = .014$, one-tailed testing) followed by the first subscale (anticipatory worry vs. uninhibited optimism; high responders: M/S.D. = 4.2/2.7, low responders: M/S.D. = 5.8/2.5; $t_{(38)} = 1.9$, $P = .029$, one-tailed testing), the third subscale (shyness with strangers; high responders: M/S.D. = 3.3/2.0, low responders: M/S.D. = 4.5/2.5; $t_{(38)} = 1.7$, $P = .049$, one-tailed testing), and the fourth subscale (fatigability and asthenia; high

responders: M/S.D. = 2.6/2.0, low responders: M/S.D. = 3.8/2.6; $t_{(38)} = 1.6$, $P = .057$, one-tailed testing).

Discussion

One important finding of this study is the observed relation between harm avoidance and prolactin response to the serotonergic challenge drug fenfluramine supporting Cloninger's personality model which relates harm avoidance to serotonergic function. In Cloninger's (1987) theoretical conceptualization, harm avoidance is closely related to the definition of Behavioral Inhibition or Anxiety proposed by Gray (1982). The data of the present study also support Gray's view that serotonin functioning is related to anxiety-related traits.

This study demonstrates that decreased serotonergic function – as neuroendocrinologically indicated by a decreased prolactin response after fenfluramine – is inversely associated with individual differences in harm avoidance. Additionally, the results show that subjects with low prolactin responses after d,l-fenfluramine scored higher in extraversion and venturesomeness than subjects with high prolactin responses. Since harm avoidance is substantially correlated to neuroticism ($r = .64$, $P < .001$; see also Weyers et al., 1995; Krebs et al., 1998), and since there is a tendency toward higher neuroticism scores in low prolactin responders, the observed relation between harm avoidance and prolactin response after d,l-fenfluramine appears consistent with a report of an inverse correlation between the prolactin response to d,l-fenfluramine and the trait of neuroticism as measured by the NEO personality inventory (Manuck et al., 1998).

In general, these results also confirm Hennig et al. (2000), who reported that blunted prolactin response after d-fenfluramine are accompanied by high values in harm avoidance. However, our results indicate differences in all subscales of harm avoidance and not only in the subscale "fatigability and asthenia".

The positive association between the prolactin responses and extraversion, as well as venturesomeness, may seem contradictory. But considering the significant intercorrelations between these three personality characteristics, this result seems to be less unlikely: harm avoidance is inversely associated with extraversion ($r = -.52$) and venturesomeness ($r = -.40$), whereas the relationship between the latter is significantly positive ($r = .44$). Looking at the item-level one can conclude that subjects with low prolactin responses to fenfluramine tend to view themselves as socially withdrawn and unassertive; they avoid risks and tend to be cautious. In contrast, subjects with high prolactin responses to fenfluramine tend to see themselves as risk loving and gregarious.

In this context one could argue that the relationship between prolactin responses to d,l-fenfluramine and extraversion and venturesomeness may be caused by the fact that d,l-fenfluramine is not as selective a probe as originally thought; it causes the release of dopamine and noradrenaline as well as serotonin (Mitchell and Smythe, 1991; Rowland and Carlton, 1986). This

poses a potential problem because prolactin secretion by the pituitary gland is regulated mainly through the inhibitory effect of dopamine (Ben-Jonathon, 1985). The effects of fenfluramine on prolactin secretion appear to be specifically mediated by serotonergic neurons terminating in the hypothalamus (Quattrone et al., 1983; Fuller et al., 1982).

However, traits identified as being related to dopaminergic responsiveness (e.g. extraversion) are only marginally correlated with serotonin-induced changes in prolactin (Depue et al., 1994), and data discussed by Zald and Depue (2001) makes evident that the prolactin response to d,l-fenfluramine almost exclusively derives from serotonin specific effects of the d-isomer.

The data presented are in accordance with the view proposed by several authors that serotonergic functioning modulates both positive (e.g. extraversion) and negative affective processing (e.g. neuroticism) (reviewed in Depue and Collins, 1999). In accordance with this conception, Zald and Depue (2001) found that individual differences in serotonin functioning are associated with the magnitude of self-reported positive and negative affect. They reported a significant inverse correlation between prolactin response to d,l-fenfluramine and mean ratings of both positive and negative affect.

Several studies investigating the association between impulsiveness and the prolactin responses to fenfluramine suggested a blunted response being correlated to psychometric measures of impulsivity (e.g. Evans et al., 2000; Cherek and Lane, 2000). The results of this study could not verify such a relationship. Perhaps the main reason for this discrepancy is the fact that the subjects of our sample were carefully controlled for co-morbid psychopathology. Especially great care was taken to exclude all subjects with antisocial personality disorders.

For this reason, the impulsiveness scores of the present sample do not differ significantly from the norm values published by Eysenck et al. (1990). It appears that the association between the prolactin response to fenfluramine and impulsivity becomes significant at I7 impulsiveness scores substantially larger than the scores yielded here (Evans et al., 2000).

One limitation of the study presented here is that the subjects do not seem to have reached their peak rise by 210 min. Though improbable, it can not be entirely ruled out that the responses of the low responders are delayed rather than blunted.

The discussion indicates that the relationship between personality and serotonergic neurotransmission may not be specific to alcoholism. Nevertheless, this relationship might be important for the treatment of alcohol-dependent individuals because it can be implemented in a complementary fashion with a view toward a combined psycho- and pharmacotherapeutical intervention with a better person-therapy-fit.

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Authors' address: H.-G. Weijers, Ph.D., Addiction Research Unit, Department of Psychiatry, University of Würzburg, Föchsleinstrasse 15, D-97080 Würzburg, Federal Republic of Germany, e-mail: weijers@mail.uni-wuerzburg.de